REMARKS

The Remarks are unchanged from the September 12, 2008 response.

Claims 1 - 8 were pending in the application. Claims 1, 2, and 4 - 8 have been cancelled by the amendments presented herein. Claim 3 has been amended. New claim 9 has been added. No new matter has been added. Support for the amendments to the claims can be found in the specification and claims as originally filed. Support for new claim 9 can be found in Example 3.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Information Disclosure Statement

The Examiner has indicated several informalities in previously filed Information Disclosure Statements. These informalities will be addressed in a later filed IDS.

Claim Objections

The Examiner has objected to claims 1 and 3 for minor informalities. The Examiner indicates that "the claims recite the non-elected polymorphism of item (4), and are not limited to the elected combination of all three polymorphisms (1) – (3) (and) (t)he claims should be amended such that they are directed to the elected invention." (Office Action, p.4).

Claim 1 has been cancelled. Claim 3 has been amended to be directed to the elected invention, the combination of all three polymorphisms (1) – (3). Applicants respectfully request withdrawal of the objection.

Rejection of Claim 3 Under 35 USC 112, second paragraph

The Examiner has rejected claim 3 under 35 USC 112, second paragraph, as being indefinite. In particular, the Examiner argues that "claim 3 is indefinite because it is not clear whether the claim is drawn to a method 'for diagnosing the risk for hypertension' as set forth in the preamble of the claim, or to a method in which 'a genetic risk for hypertension is merely assessed,' as set forth in the final process step." (Office Action, p.5). Applicants respectfully disagree.

As amended, claim 3 recites "a method for assessing the genetic risk for hypertension."

Thus, Applicants submit that the instant claim is definite as written and the rejection be withdrawn.

Rejection of Claims 1 and 3 Under 35 USC 112, first paragraph

The Examiner has rejected claims 1 and 3 under 35 USC 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner argues that "the specification, while being enabling for methods of genotyping a human subject by analyzing the 3 polymorphisms of the elected combination in a nucleic acid sample from a human subject, and for methods of diagnosing hypertension risk in which the combination of Gpla A1648G, CCR2 G109A, and ApoCIII C110T polymorphisms are detected as being indicative of hypertension risk in human male subjects, does not reasonably provide enablement for methods of genotyping any type of nucleic acid sample, or for methods of diagnosing hypertension risk in subjects other than human males." (Office Action, p.5 – 6).

Claim 1 has been cancelled. Claim 3 has been amended to recite a method for assessing the genetic risk for hypertension of a **human male subject** comprising the steps of (i) analyzing the polymorphisms (1) to (3) in a nucleic acid sample from the

human male subject, where the polymorphisms comprise (1) a polymorphism at the **base number position 1648 of the glycoprotein Ia gene**; (2) a polymorphism at the **base number position 190 of the chemokine receptor 2 gene**; and (3) a polymorphism at the **base number position 1100 of the aplipoprotein C-III gene**; (ii) determining, based on the information about polymorphism which was obtained in the step (i), the genotype in the nucleic acid sample of the human male subject; and (iii) assessing, based on the genotype determine, a genetic risk for hypertension of the human male subject. (emphasis added).

The MPEP states that the determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing a combination of factual considerations: the breath of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples, and the quantity of experimentation necessary. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

The Examiner argues that "(i)t is unpredictable as to whether one of skill in the art could use Applicants' invention in a manner reasonable commensurate with the claims...each of the claims 1 and 3 encompass detecting/ determining a genotype for each of a polymorphism at the base number position 1648 of the glycoprotein 1a gene...a polymorphism at the base number position 190 of the chemokine receptor 2 gene...and a polymorphism at the base number position 1100 of the apolipoprotein C-111 gene." (Office Action, p.7). The Examiner argues that "in the context of the instant invention, determination of a genotype requires the existence of more than one allele for each position being analyzed, in order that a genotype may be established for the sample being assayed...(h)owever the instant claims encompass genotyping any type of nucleic acid sample, while the specification and the prior art establish the existence of the relevant poymorphisms in human nucleic acids." (Office Action, p.7 – 8).

Applicants have amended the claims to recite a method for assessing the genetic risk for hypertension of a **human male subject**. The Examiner points out

support for identifying polymorphisms in these genes in human male subjects in the specification (Office Action, p.7).

The Examiner argues that "while the teachings of the specification would enable one of skill in the art to diagnose hypertension risk in a Japanese male subject by detecting the combination of GpIa A1648G, CCR2 G190A, and ApoCIII C1100T polymorphisms in a nucleic acid sample from the subject, the teachings of the specification are not enabling with regard to other types of subjects, or with regard to a relationship between hypertension risk and variants at GpIa 1648, CCR2 190, or ApoCIII 1100 other than the specific ones noted above." (Office Action, p.9). Applicants disagree.

The instant invention is based on large scale association study for single nucleotide polymorphisms (SNPs) in an effort to predict risk of hypertension. As taught in the specification, the instant invention analyzes selected SNPs and further identifies three gene polymorphisms: GPIa gene polymorphism, CCR2 gene polymorphism, and Apo C-III gene polymorphism. The combination of polymorphisms recited in the instant invention exhibits very high odds ratios, as set forth in the Table in Figure 6. The Examiner admits that "the techniques required to carry out genotyping are routine in the art, and the skill level of one of ordinary skill in the art is high." (Office Action, p.8). Accordingly, as Applicants have limited the claims to the three gene polymorphisms taught in the Examples as susceptibility loci for hypertension, and the Examiner admits that the techniques of genotyping are routine in the art, thus it would be routine for one of skill in the art to genotype candidate SNPs of the GPIa gene polymorphism, CCR2 gene polymorphism, and Apo C-III gene polymorphism as claimed, to assess the genetic risk for hypertension of a human male subject.

Taken together, the teachings of the specification and the knowledge of the skilled practitioner enables practice of the full scope of the claimed invention, without having to resort to undue experimentation.

Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection of Claim 1 Under 35 USC 102(b)

The Examiner has rejected claim 1 under 35 USC 102(b) as being anticipated by Yamada et al. (New England Journal of Medicine, 347 (24): 1916 – 1923. December 12, 2002).

Claim 1 has been cancelled making this rejection now moot.

Rejection of Claims 1 and 3 Under 35 USC 102(a)

The Examiner has rejected claims 1 and 3 under 35 USC 102(a) as being anticipated by Izawa et al. (Hypertension 41: 1035 – 1040 [published on line March 2003]). Applicants respectfully traverse this rejection.

The Examiner indicates that "the rejection may be overcome by establishing priority of the invention to September 25, 2002 by filing a certified translation of Applicants' priority document." (Office Action, p.12).

Applicants submit herein a certified translation of the priority document establishing a priority date of September 25, 2002 Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claim 1 Under 35 USC 103(a)

The Examiner has rejected claim 1 under 35 USC 103(a) as being unpatentable over Kroll et al. (Thromb Haemost 83:392 – 396. 2000) in view of Groenendijk et al. (J of Lipid Research 42: 188 – 194. 2001) and Gonzalez et al. (Genes and Immunity 2: 191 – 195. 2001). Applicants respectfully traverse the rejection.

Claim 1 has been cancelled. The pending claims 3 and 9 recite a method for assessing the genetic risk for hypertension of a human male subject comprising the steps of (i) analyzing the polymorphisms (1) to (3) in a nucleic acid sample from the human male subject.

The Examiner argues that "Kroll et al. disclose analyzing the Gpla gene A1648G polymorphism...in different subpopulations of a group of human subjects, and disclose that the A1648G variant is associated with the presence and extent of coronary artery disease in low risk patient subgroups." (Office Action, p.14).

The Examiner argues that "Groenendijk et al. disclose analyzing the apoC-III gene C1100T polymorphism...in different subpopultions of human subjects, and disclose that the T1100 variant is associated with elevated plasma triglycerides, and that this variant has been associated with atherosclerosis." (Office Action, p.14).

The Examiner argues that "Gonzalez et al. disclose analyzing the CCR2 gene polymorphism encoding V64I...in different subpopulations of human subjects, and disclose that while this polymorphism was not found to be associated with myocardia infarction, CCR2 is known to be important in the 'initiation of atherosclerosis.'" (Office Action, p.15).

The Examiner argues that "(t)he Kroll et al., Groenendijk et al and Gonzalez et al references thus each disclose genotyping one of the polymorphisms of the elected invention in the context of investigating factors contributing to diseases of the circulatory system (and) the prior art does not disclose genotyping these three polymorphisms together in a single method as required by the instant claim. However, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to have done so." (Office Action, p.15). The Examiner argues that "(e)ach of the references discloses the analysis of multiple different polymorphisms in investigating the association of genotypes and haplotypes with disease (and) an ordinary artisan would have been motivated to have analyzed together any group of polymorphisms with known or suspected associations with one or more diseases of the circulatory system." (Office Action, p.15). Applicants disagree.

The Kroll reference determines an association of the A1648G polymorphism of the platelet collagen receptor in coronary artery disease in certain defined patient groups. Kroll et al analyze "the clinical significance of the GPIa A1648G polymorphism in patients with CAD and acute myocardial infarction (AMI) in a population of 2163 male individuals whose coronary anatomy was exactly defined by coronary angiography." (p.392).

Coronary Artery Disease (CAD) and hypertension are different diseases. Although it is known in the art that CAD contributes to hypertension, no direct, causal link between hypertension and CAD is known. CAD is a type of heart disease that includes a variety of diseases. CAD includes arteriosclerosis (the hardening of medium and large arteries, of which the most common form is atherosclerosis), ischemic heart disease, narrowing of the arteries and congential defects of the arteries. There are many factors that contribute to the development of CAD, including environmental factors and genetic factors. Smoking, high blood pressure (hypertension), hi blood cholesterol (hyperlipidemia), high amounts of sugar in the blood due to insulin resistance or diabetes, metabolic syndrome, weight, age, family history, stress, lack of physical activity, alcohol are among possible contributing risk factors for CAD identified by the National Heart, Lung, and Blood Institute (available on the world wide web at nhlbi.nih.gov/health/dci/Diseases/Cad/CAD_Causes.html). Likewise, there are no clear underlying causes for hypertension. Hypertension may be a result of genetic factors, gender, underlying diseases or conditions, medication, environmental factors and lifestyle. Applicants attach Appendix A, which is a flow chart that depicts the multiple causes that contribute to coronary arteriosclerosis and hypertension. Clearly, the relationship between CAD and hypertension is not direct. Thus, although CAD is known to contribute to hypertension, hypertension is not known to cause CAD, and a risk of hypertension does not translate to a risk for CAD.

CAD, as taught in the Kroll et al. reference, refers to arteriosclerotic coronary artery disease, and is defined as follows:

> coronary vessels with at least 50% stenosis were defined as diseased (and) (b)y means of coronary

> angiography, the study population was divided into subjects without any angiographical signs of CAD or with coronary arterial stenosis less than 50% and individuals with single, double or tripe vessel disease. (p.392)

The instant invention is directed to a method for assessing diagnosing the genetic risk for **hypertension** of a human male subject. As pointed out above, hypertension, while a risk factor for CAD, is not the same disease as CAD, and there is no knowledge in the art that CAD is a risk factor for hypertension. Although hypertension can lead to a multitude of diseases and conditions, including CAD, it can also lead to heart failure, stroke, kidney failure, and other health problems. Nowhere does the Kroll et al. reference teach that the GPIa A1648G polymorphism can be used to determine an association with hypertension. The patient population chosen by Kroll et al., e.g. patients with CAD and acute myocardial infarction (AMI), were chosen for the purpose of determining association of the GPIa polymorphism with CAD.

It would not be predictive that a gene polymorphism which has been identified to associate with arteriosclerotic CAD, as taught in the Kroll et al. reference, would also associate with hypertension. Thus it would not be obvious for an ordinary artisan to predict that the gene polymorphism which has been identified to associate with arteriosclerotic CAD also associates with hypertension, any more than the polymorphism associates with a multitude of other risk factors and diseases, of which there are many. Accordingly, there is no teaching or suggestion in the Kroll et al. reference of this association, or to make this association.

None of the Groenendijk or Gonzalez references cures this defect. Neither Groenendijk nor Gonzalez teaches or suggests the method for assessing the genetic **risk for hypertension of a human male subject comprising the steps of (i) analyzing the polymorphisms (1) to (3)** in a nucleic acid sample from the human male subject.

The Examiner argues that each disclose genotyping one of the polymorphisms of the elected invention in the context of investigating factors contributing to diseases of the circulatory system...(and) it would have been prima facie obvious to one of ordinary

skill in the art at the time of the invention was made to have done so." (Office Action p.15).

As described above, a risk of hypertension does not translate to a risk for any cardiovascular disease or disorder. Although it is known that that hypertension is a risk factor of arteriosclerosis, there is no mutual association between arteriosclerosis and hypertension. One of ordinary skill in the art would not be motivated to predict that the gene polymorphism which has been identified to associate with any cardiovascular disease, for example arteriosclerosis, also associates with hypertension. Accordingly the gene polymorphisms identified by Groenendijk et al or Gonzalez et al would not be predicted to also associate with hypertension. Moreover, none of the combination of the cited references teaches or suggests method for a method for assessing the genetic **risk for hypertension of a human male subject comprising the steps of (i) analyzing the polymorphisms (1) to (3)** in a nucleic acid sample from the human male subject as instantly claimed.

The instant invention is supported by the results of a large scale association study involving 574 male patients and 533 male controls (see, e.g., Figure 5). No study described in the art to date has examined association in such a large population group, and thus provides a highly credible diagnostic outcome.

The instant invention analyses three gene polymorphisms of: (1)GPIa gene polymorphism; (2)CCR2 gene polymorphism; and (3)Apo C-III gene polymorphism. The combination of polymorphisms recited in the instant invention exhibits very high odds ratios, as follows below and are set forth in Figure 6 (Table).

(i)Odds ratios of polymorphism of GPIa gene (singularly)

Odds ratio of recessive model is 0.6 (P-value is 0.0266). The odds ratio is to be calculated as dominant model in which A allele is a risk allele, meaning odds ratio is 1.7 (reciprocal number of 0.6) in a case where A allele is detected. The odds ratio of each genotype is AA 1.7, AG 1.7 and GG 1.0.

(ii)Odds ratios of polymorphism of CCR2 gene (singularly)

Odds ratio of recessive model is 1.8 (P-value is 0.0151), meaning odds ratio is 1.8 in a case where the genotype is AA. The odds ratio of each genotype is GG 1.0, GA 1.0 and AA 1.8.

(iii)Odds ratios of polymorphism of Apo C-III gene (singularly)

Odds ratio of recessive model is 0.8 (P-value is 0.0373). The odds ratio is to be calculated as dominant model in which C allele is a risk allele, meaning odds ratio is 1.3(reciprocal number of 0.8) in a case where C allele is detected. The odds ratio of each genotype is CC 1.3, CT 1.3 and TT 1.0.

(iv)Odds ratios of the combination of three polymorphisms

Odds ratio of a combination of polymorphisms approaches the value calculated by multiplying the odds ratios of polymorphisms. When the three polymorphisms are combined, the combination of AA or AG (polymorphism of GPIa gene), AA (polymorphism of CCR2 gene) and CC or CT (polymorphsm of Apo C-III gene) shows a maximum odds ratio whose approximate value is "1.7 x 1.8 x 1.3 = 3.98".

As shown in the data above and in Figure 6, the combination of the three polymorphisms shows a strong association with hypertension. Accordingly, analysis of the **combination of these three polymorphisms** makes it possible to diagnose a risk of hypertension with high accuracy and high predictability. Nowhere does the cited art, singularly or together, teach or suggest the method for assessing the genetic **risk for hypertension of a human male subject comprising the steps of (i) analyzing the polymorphisms (1) to (3)** in a nucleic acid sample from the human male subject, as instantly claimed.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

CONCLUSION

In view of the above arguments and amendments, Applicants believe the pending application is in condition for allowance. If a phone call with the Applicant's attorney would help to expedite prosecution, the Examiner is urged to contact the undersigned.

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Respectfully submitted,

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Encls: *Enclosures were submitted on September 12, 2008 and will not be resubmitted.*
Appendix A: The Causes/Mechanism of Microcardial Infarction (1 page)
Certified Translation of Priority Document (136 pages)
Verification of Translation (1 page)